September 17, 2004
Confidential

Appl. No	:	09/646,110
Applicant	:	Dyck et al.
Filed	:	November 5, 2001
Title	:	ALIPHATIC AMINO CARBOXYLIC AND AMINO PHOSPHONIC ACIDS, AMINO NITRILES AND AMINO TETRAZOLES AS CELLULAR RESCUE AGENTS
TC./A.U.	:	1625
Examiner	:	Hector M. Reyes
Docket No.	:	10242-34

Honorable Commissioner for Patents
P. O. Box 1450
Alexandria, Virginia 22313–1450

DECLARATION UNDER 37 CFR §1.132 OF MARK D. BERRY TRAVERSING GROUNDS OF REJECTION

Sir:

Under 37 C.F.R. §1.132 and regarding the rejection of previous claims 25-31 (now claims 32-35) under 35 U.S.C. § 112, first paragraph, for lack of enablement, I declare:

1. I am an Assistant Professor in the Department of Chemistry at Brandon University, Brandon, Manitoba, Canada.

2. Prior to my current position, I was Senior Scientific Officer and head, Target Identification and Model Development at Alviva Biopharmaceuticals, Saskatoon, Saskatchewan, Canada. My education and professional experience are described in further detail in my curriculum vitae, a copy of which is attached as Appendix A.

3. During my employment at Alviva Biopharmaceuticals I was responsible for developing and performing in vitro and in vivo screens for drug candidates, in particular in the field of apoptosis/programmed cell death with particular reference to neurodegenerative diseases. In this capacity, I was involved with and responsible for testing the compounds described and claimed in U.S. patent application number 09/646,110 (hereinafter "the application").

4. I have read and understood the contents of the application.

5. I have read and understood the Office Action, dated June 23, 2004, for the application.

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6. In particular I note the Examiner's objection to previous claims 25-31 (now claims 32-35) under 35 USC §112, first paragraph as not being enabling for all of the compounds within the scope of these claims. I respectfully disagree with the Examiner for the reasons that follow.

7. Experiments have been conducted by me or under my supervision which demonstrate that certain compounds listed in the application as being not active in an in vitro assay for cellular rescue, actually have activity in an in vivo assay for cellular rescue. The details and results of these experiments are summarized below.

8. Certain compounds within the scope of previous claims 25-31 (now claims 32-35) of the application were tested for activity in decreasing lesion volume when administered by either oral or intra-peritoneal routes, with the first dose administered 3 hours following lesion, in a rat pial artery disruption model of stroke. The study employed male Wistar rats initially weighing between 220 and 410g. Animals were randomly assigned to treatment groups on the day of surgery, with a maximum of 10 surgeries performed per day. On each day at least one control animal (lesion with drug treatment replaced with vehicle administration) was used. Following anaesthesia animals were placed in a stereotaxic frame and a 5mm diameter hole drilled in the skull 1mm lateral to bregma. The dura were carefully removed and all terminal pial arteries disrupted by pinching with fine forceps. The wound area was cleaned, skin incision closed and topical anaesthetic plus analgesic applied. Animals were housed individually, allowing a card identification system to be employed. After surgery animals were returned to their home cage for recovery. Three hours following surgery animals were treated by either intra-peritoneal or oral administration of the test compound at various doses, or vehicle (PBS). Drug/vehicle treatment was repeated 24 hours after initial drug administration, with animals killed by anaesthetic overdose 24 hours following final drug administration. The brain was removed, immersion fixed in FAM (40% formaldehyde; glacial acetic acid; methanol: 1;1;8: v;v;v) and stored in FAM until paraffin embedded. Slices (20□m thick) were cut from paraffin embedded brains throughout the entire extent of the lesion. Slices were stained with haematoxylin and eosin, and lesion volume determined microscopically.

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9. The results for the test compounds obtained from the in vivo study are as follows:

Test Compound	Rescue (R) or No Rescue (X)*
Carboxylic Acids	
R-3-(2-heptylamino)propionic acid	R
S-3-(2-heptylamino)propionic acid	X
R-3-(2-pentylamino)propionic acid	R
S-3-(2-pentylamino)propionic acid	X
R-4-(2-heptylamino)butanoic acid	R
3-(2-propylamino)propionic acid	R
3-(1-hexylamino)propionic acid	R
Carboxylate Esters	
Methyl R-3-(2-heptylamino)propionate	R

* Dose of 1 mg/kg

10. The above results demonstrate that the compound, R-3-(2-pentylamino)propionic acid, possesses cellular rescue activity in vivo. This is in contrast to the in vitro results obtained and presented in the application, where this compound was listed as a non-rescuer.

11. The results presented above further demonstrate that R-4-(2-heptylamino)butanoic acid, a compound not specifically disclosed in the application, but within the scope of the claims and representing an example of a compound where n = 3, was shown to have cellular rescue activity.

12. I submit that foregoing results demonstrate the vulnerability of in vitro bioassays to occasional, often unexpected, glitches, which contributes to the apparent unpredictability in the activity of the claimed compounds.

13. I further submit that the application does support a method for treating diseases in which cell death occurs by apoptosis by administering a compound of Formula I as defined in previous claims 25-31 (now claims 32-35).

14. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and, further, that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under

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Section 1001 of Title 18 of the United States Code and that such a wilful false statement may jeopardize the validity of the application or any patent issuing thereon.

19/Sept/04
Date

Mark D. Berry

Appendix A

Curriculum Vitae

Personal

Name	Mark Darren Berry	
Address-home	2133, Ewart Avenue Saskatoon Saskatchewan Canada S7J 1X8	**-work** Department of Chemistry Room 4-12, J.R. Brodie Science Centre Brandon University Brandon, Manitoba Canada, R7A 6A9
Phone -home	(306)374-8837	**-work** (204)727-9775
Fax -home	(306)374-8837	**-work** (204)
e-mail-home	markberry@sasktel.net	**-work** berrym@brandonu.ca
Date of Birth	23rd March 1968	
Nationality	British (Canadian landed immigrant)	

Education/Employment

2004 **Assistant Professor**
Department of Chemistry, Brandon University
Brandon, Manitoba, Canada

Responsibilities:
- Teaching undergraduate degree courses in Chemistry and Biochemistry
- Supervision of undergraduate project thesis
- Supervision of undergraduate biochemistry laboratory sessions

2003 **Senior Scientific Officer**
ALviva Biopharmaceuticals Inc.
Saskatoon, Saskatchewan, Canada

2000-2002 **Head, Target Identification and Model Development**
ALviva Biopharmaceuticals Inc.
Saskatoon, Saskatchewan, Canada

Responsibilities:

- Supervision of research scientists and technicians
- Development of screening and disease specific *in vitro* and *in vivo* models
- Investigation of the mechanism of action of lead compounds
- Assessment of competitor technologies
- Determination of competitive advantages of compound library
- Writing of final project reports
- Writing technical due diligence document
- Identification of external research scientists for collaborative projects
- Presentation of information to potential investors and collaborators
- Design of new research laboratories and animal facilities
- Formation of the Animal Care Committee
- Presentation of data at scientific meetings

Research specialization:

- apoptosis/programmed cell death with particular reference to neurodegenerative diseases
- targets of anti-apoptotic drug action.
- modulation of central monoaminergic neurotransmission
- trace amines
- general pharmacology
- modulation of cancer chemotherapeutics

Courses/Training:

- GLP training
- animal care and handling certification
- manager/supervisor conference

1999-2000 Senior Research Scientist
ALviva Biopharmaceuticals Inc.
Saskatoon, Saskatchewan, Canada

Responsibilities:

- Supervision of research technicians
- *In vitro* and *in vivo* screening of compound library
- Investigation of the mechanism of action of lead compounds
- Presentation of information to potential investors and collaborators
- Presentation of data at scientific meetings

1999-present Adjunct Professor
Department of Psychiatry
University of Saskatchewan
Saskatoon, Saskatchewan, Canada

Responsibilities:

- Supervision of research technicians
- Supervision of graduate students
- Teaching graduate student level classes

1996-1999 Post-doctoral Research Associate
Neuropsychiatry Research Unit
University of Saskatchewan
Saskatoon, Saskatchewan, Canada

Responsibilities:

- Supervision of graduate and undergraduate students
- Teaching graduate student level classes

Research Specialization:

- Anti-apoptotic effects of endogenous polyamines
- Anti-aging effects of anti-apoptotic compounds
- Role of glyceraldehyde-3-phosphate dehydrogenase in apoptotic cascades

1993-1995 Post-doctoral Researcher
Department of Pharmacology
Ohio State University
Columbus, Ohio, USA

Research Specialization:

- Regulation of aromatic L-amino acid decarboxylase

1989-1993 Graduate student
Neuropsychiatry Research Unit
University of Saskatchewan
Saskatoon, Saskatchewan, Canada

Qualifications Ph.D. (Neuropsychiatry). "The neuromodulatory effect of 2-phenylethylamine on catecholaminergic systems"
Supervisor – Dr. I. Alick Paterson
Awarded September 1993

1986-1989 Student
Department of Pharmacology
Sunderland University
Sunderland, Tyne & Wear, England

Qualifications B.Sc.(Hons.) Pharmacology (2:1[Upper second class])
Awarded June 1989

Awards/Prizes

1997 American Society for Neurochemistry Travel Award

1994-1995 The Ohio State University Parkinson's Disease Center of Excellence Post-doctoral Fellowship

1990-1993 University of Saskatchewan graduate student scholarship

1988 ICI prize for best overall second year grades, Sunderland University

Grants

1999 A.A. Boulton and **M.D. Berry**
Huntington Society of Canada Navigator Research Award. One year non-renewable. *Huntington's disease, glyceraldehyde-3-phosphate dehydrogenase and apoptosis.*

1998 **M.D. Berry**, B.A. Davis and A.A. Boulton
NRC IRAP Industrial Research Grant. *Development of lead compounds from an aliphatic propargylamine library for Alzheimer's disease and stroke.*

Editing

2003 **M.D. Berry** and A.A. Boulton
Progress in Neuropsychopharmacology and Biological Psychiatry Special Issue – Apoptosis and Neurodegenerative Diseases. 27; 197-332.

Publications

Book chapter:

2002 **M.D. Berry** and P.C. Ashe
Glyceraldehyde-3-phosphate dehydrogenase as a target for anti-apoptotic drug action. ***NeuroMethods 37: Apoptosis techniques and protocols.*** 2nd Edition. (ed. A. LeBlanc) pp. 149-161.

Papers:

2004 A. Holt, **M.D. Berry** and A.A. Boulton
On the binding of monoamine oxidase inhibitors to some sites distinct from the MAO active site, and effects thereby elicited. ***Neurotoxicology*** 25; 251-266.

M.D. Berry
Glyceraldehyde-3-phosphate dehydrogenase as a target for small molecule disease-modifying therapies in human neurodegenerative disorders. ***J. Psych. Neurosci.*** (invited commentary – in press)

M.D. Berry
Mammalian central nervous system trace amines: pharmacologic amphetamines, physiologic neuromodulators. ***J. Neurochem.*** 90; 257-271.

2003 P.C. Ashe and **M.D. Berry**
Cell death signal transduction pathways. ***Prog. Neuropsychopharmacol. & Biol. Psychiat.*** 27; 199-214.

2002 **M.D. Berry** and A.A. Boulton
Aliphatic propargylamines as symptomatic and neuroprotective treatments for neurodegenerative disorders. ***Neurotoxicol. Teratol.*** 24; 667-673.

M.D. Berry and A.A. Boulton
Aliphatic propargylamines as treatments for neurodegenerative diseases: catecholamine research – from molecular insights to clinical medicine. ***Adv. Behav. Biol.*** 53; 455-458.

2001 P.C. Ashe, **M.D. Berry** and A.A. Boulton
Schizophrenia, a neurodegenerative disorder with neurodevelopmental antecedents. ***Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*** 25; 691-707.

2000 **M.D. Berry** and A.A. Boulton
Glyceraldehyde-3-phosphate dehydrogenase and apoptosis. ***J. Neurosci. Res.*** 60; 150-154.

A.-M. Duchemin, **M.D. Berry**, N.H. Neff and M. Hadjiconstantinou
Phosphorylation and activation of brain aromatic L-amino acid decarboxylase by cyclic AMP-dependent protein kinase. ***J. Neurochem.*** 75; 725-731.

1999 R.G. Jordens, **M.D. Berry**, C. Gillott and A.A. Boulton
Prolongation of life in an experimental model of aging in *Drosophila melanogaster.* ***Neurochem. Res.*** 24; 227-233.

M.D. Berry

N^8-acetyl spermidine protects rat cerebellar granule cells from low K^+ induced apoptosis. ***J. Neurosci. Res.*** 55; 341-351.

M.D. Berry

R-2HMP, an orally active agent combining independent anti-apoptotic and MAO-B inhibitory activities. ***CNS Drug Rev.*** 5; 105-124.

D. Zhang, **M.D. Berry**, I.A. Paterson and A.A. Boulton
Loss of mitochondrial membrane potential is dependent on the apoptotic program activated: prevention by R-2HMP. ***J. Neurosci. Res.*** 58; 284-292.

1996 **M.D. Berry**, A.V. Juorio, X.-M. Li and A.A. Boulton
Aromatic L-amino acid decarboxylase: a neglected and misunderstood enzyme. ***Neurochem. Res.*** 21; 1075-1087.

1994 **M.D. Berry**, A.V. Juorio and I.A. Paterson
The functional role of monoamine oxidases A and B in the mammalian central nervous system. ***Prog. Neurobiol.*** 42; 375-391.

M.D. Berry, A.V. Juorio and I.A. Paterson
Possible mechanisms of action of (-)deprenyl and other MAO-B inhibitors in some neurologic and psychiatric disorders. ***Prog. Neurobiol.*** 44; 141-161.

M.D. Berry, E. Scarr, M.-Y. Zhu, I.A. Paterson and A.V. Juorio
The effects of administration of monoamine oxidase-B inhibitors on rat striatal neuron responses to dopamine. ***Br. J. Pharmacol.*** 113; 1159-1166.

1991 I.A. Paterson, A.V. Juorio, **M.D. Berry** and M.-Y. Zhu
Inhibition of monoamine oxidase-B by (-)deprenyl potentiates neuronal responses to dopamine agonists but does not inhibit dopamine catabolism in the rat striatum. ***J. Pharmacol. Exp. Ther.*** 258; 1019-1026.

Patents:

1997 **M.D. Berry**, B.A. Davis, I.A. Paterson, D.A. Durden and A.A. Boulton
N-alkanoyl- and N-alkylpolyamines as cellular rescue agents and modulators of antineoplastic action. *United States Provisional Application #60/110,167, filed 27 November 1998.* Re-filed 2001.

Abstracts (last 3 years) – 30 total

2002 **M.D. Berry**, A. Holt, K. Williamson, R. Ortmann and A.A. Boulton
Small molecule aliphatic amines as centrally available, non-toxic neural rescue agents for use in chronic and acute degenerative disorders. ***Society for Neuroscience*** (Orlando, Florida).

M.D. Berry, L.Osman, K. Williamson, D. Douglas and C. Weeks-Levy
Administration of aliphatic propargylamines at 7 hours following permanent focal ischaemia show rescue of neurons. ***Keystone Symposium:*** *Stroke – Molecular, Cellular, Pharmacologic and Development of New Therapeutics* (Taos, New Mexico).

2001 **M.D. Berry**, L. Osman, K. Williamson and A.A. Boulton
Aliphatic compounds rescuing from permanent focal ischaemia when administration is delayed until 5 hours after lesion. ***American College for Neuropshychopharmacology*** (Waikoloa, Hawaii).

M.D. Berry, L. Osman, K. Williamson, D. Douglas and C. Weeks-Levy
Aliphatic propargylamines as potent rescue agents in an in vivo stroke model. ***2nd Mechanisms of Cell Death and Disease Conference:*** *Advances in Therapeutic Intervention* (Falmouth, Massuchusettes).

M.D. Berry, L. Osman, K. Williamson and D. Douglas
Aliphatic propargylamines rescue from permanent focal ischaemia when administered 5 hours following insult. ***Society for Neuroscience*** (San Diego, California).

R.G. Jordens, **M.D. Berry** and A.A. Boulton
Premature loss of climbing ability in *Drosophila* aging models. ***Society for Neuroscience*** (San Diego, California).

M.D. Berry and L.D. Hanson
Aliphatic propargylamines and their derivatives: *in vitro* rescue from β-amyloid (25-35) induced toxicity. ***5th International Conference on Progress in Alzheimer's and Parkinson's disease*** (Kyoto, Japan).

M.D. Berry, D. Douglas, L. Osman, K. Williamson and A.A. Boulton
Rescue from focal ischaemia by novel aliphatic propargylamines and their metabolites. ***Joint ISN/ASN meeting*** (Buenos Aires, Argentina).

R.G. Jordens, **M.D. Berry** and A.A. Boulton
Effects of galactose substitution on the expression of superoxide dismutase and catalase in a *Drosophila melanogaster* aging model. ***Joint ISN/ASN meeting*** (Buenos Aires, Argentina).

Students

Doctorate

1996-2002 Robert G. Jordens, co-supervisor (with Dr. A.A. Boulton)
"The effects of galactose ingestion and selected pharmacological agents on lifespan, climbing ability, and the expression of *superoxide dismutase* and *catalase* in *Drosophila melanogaster*"
Ph.D. awarded September, 2002

1998-2000 Dajiang Zhang, co-supervisor (with Dr. A.A. Boulton)

"Anti-apoptotic actions of R-2HMP in cerebellar granule cells: changes of mitochondrial membrane potential and sub-cellular GAPDH protein"
Ph.D. awarded September, 2000.

Masters

1998-2000 Colleen Fennig, co-supervisor (with Dr. A.A. Boulton)
"Putative anti-apoptotic effects of anti-psychotics on cerebellar granule cells"
M.Sc. awarded September, 2000.

Undergraduate

2004 Jason Lamontagne
"Detection and quantification of trace amines in foodstuffs implicated in the initiation of migraine attacks"
Undergraduate honours degree thesis

1996 Robert G. Jordens (summer student), co-supervisor (with Dr. A.A. Boulton)

Teaching

2004 18.160 General Chemistry. Brandon University
18.363 Biochemistry I. Brandon University
18.174/74.174 Introductory Physical Science (Chemistry section). Brandon University

2002 Psiat 850.6 Neuropsychiatry (Neurophysiology section) University of Saskatchewan.

ch 400 Guest lecturer ("Drug development in a Start-up Biopharmaceutical Company") University of Saskatchewan

2000 Psiat 898.3 Special topics in Neuropsychiatry ("Neurobiology of human neurodegenerative diseases"). University of Saskatchewan.

Psiat 850.6 Neuropsychiatry (Neurophysiology section) University of Saskatchewan.

1998 Psiat 850.6 Neuropsychiatry (Neurophysiology section) University of Saskatchewan.

Committees

2002-2003 AL*viva* Biopharmaceuticals Animal Care Committee

2000-2002 AL*viva* Biopharmaceuticals Safety Committee

1997-2002 Graduate student advisory committee member for R.G. Jordens. Awarded Ph.D. September, 2002.

1997-2000 Graduate student advisory committee member for D. Zhang and K. Tieu. Both awarded Ph.D. September 2000.

1998-2000 Graduate student advisory committee member for C. Fennig. Awarded M.Sc. September 2000.

1994-1995 Executive board member of the Ohio State University Health Sciences Post-doctoral Society.